

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> : <b>C07C 59/52, 51/48, 51/487, C07B 57/00</b>		A1	(11) International Publication Number: <b>WO 94/14746</b> (43) International Publication Date: <b>7 July 1994 (07.07.94)</b>
<p>(21) International Application Number: <b>PCT/NL93/00277</b></p> <p>(22) International Filing Date: <b>23 December 1993 (23.12.93)</b></p> <p>(30) Priority Data: <b>9202248 23 December 1992 (23.12.92) NL</b></p> <p>(71) Applicant (<i>for all designated States except US</i>): TECHNISCHE UNIVERSITEIT DELFT [NL/NL]; Julianalaan 136, NL-2628 BL Delft (NL).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): HOEFNAGEL, Antho-nius, Johannes [NL/NL]; Technische Universiteit Delft, Julianalaan 136, NL-2628 BL Delft (NL). VAN BEKKUM, Herman [NL/NL]; Technische Universiteit Delft, Julianalaan 136, NL-2628 BL Delft (NL).</p> <p>(74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octrooibureau, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).</p>		<p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> <i>In English translation (filed in Dutch).</i></p> <p>(54) Title: PROCESS FOR SEPARATING THE ORTHO- AND PARA- ISOMERS OF HYDROXYMANDELIC ACID OR A SALT THEREOF, THE ISOMERS THUS OBTAINED, THE USE OF THE ORTHO-ISOMER FOR THE PREPARATION OF EDDHA</p> <p>(57) Abstract</p> <p>The invention relates to a method for separating the ortho- and para-isomers of hydroxymandelic acid or a salt thereof. For that purpose the starting material is a solid mixture of these ortho- and para-isomers in the alkali metal salt form. This mixture is extracted with a polar, aprotic, organic solvent. Then this organic solvent phase is separated from the other phase. The ortho-isomer can be recovered from the polar, aprotic, organic solvent phase and the para-isomer from the other phase.</p>	

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

PROCESS FOR SEPARATING THE ORTHO- AND PARA- ISOMERS OF HYDROXYMANDELIC ACID OR A SALT THEREOF, THE ISOMERS THUS OBTAINED, THE USE OF THE ORTHO-ISOMER FOR THE PREPARATION OF EDDHA.

The invention relates to a method for separating the ortho- and para-isomers of hydroxymandelic acid or a salt thereof, to the ortho- and para-isomers obtained by the practice of the method according to the invention, and to the 5 use of the thus obtained ortho-isomer in the preparation of  $\alpha,\alpha\text{-(1,2-ethanediylidimino)-bis-[2-hydroxy]-benzeneacetic acid}$  (EDDHA).

In the preparation of hydroxymandelic acid, for instance through the hydroxyalkylation of phenol with glyoxylic acid, 10 as a rule a mixture is produced in which substantially two isomers of this compound are present: the ortho- and para-isomers. It is a well-known problem that these two isomers are very difficult to separate.

To avoid this problem as much as possible, methods have 15 been proposed whereby, through influencing the reaction conditions, a mixture is obtained which comprises a high or, conversely, a low ratio of ortho-isomer to para-isomer.

German patent application 2,944,295 describes a method by 20 the use of which fairly pure para-hydroxymandelic acid (melting range 83-85°C) is obtained in a yield of 70-85%. According to this method, glyoxylic acid is reacted with phenol under alkaline conditions for a relatively short reaction time and at an increased temperature. It has been found (Hoefnagel et al., Recl. Trav. Chim. Pays-Bas 107 25 (1988), 242) that by the use of this method, in addition to the para-isomer, 15% ortho-hydroxymandelic acid was formed.

EP 368,696 describes the preparation of the sodium salt 30 of para-hydroxymandelic acid on industrial scale. For that purpose, a concentrated aqueous solution of glyoxylic acid is added to a six-fold to eight-fold molar excess of phenol in

the presence of a tertiary amine. This amine should be hardly water-soluble, if at all, at room temperature. According to the method described, after a reaction for 345 minutes at 20°C, and utilizing triisooctyl amine, the sodium salt of pure 5 para-hydroxymandelic acid precipitates after a 5% aqueous solution of sodium hydroxide has been added. After washing with diluted isopropanol the product is obtained in a yield of 70%.

International patent application 81/00404 also describes 10 a method whereby a solid salt of para-hydroxymandelic acid is isolated. For this purpose, phenol is reacted with glyoxylic acid in the presence of sodium or potassium hydroxide at alkaline pH. Then at neutral pH the excess phenol is removed. 15 The reaction mixture is acidified to a pH less than 3. This strongly acid solution is extracted with a water-immiscible organic solvent, for instance methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, methyl acetate or mixtures of these solvents. Finally, a salt of para-hydroxymandelic acid is precipitated from the organic solvent phase.

20 Besides the resultant yields of the para-substituted product, which are between 50 and 72% according to the examples and therefore are relatively low, no by-products are isolated. This constitutes a major loss of valuable products as well as a major burden on the environment.

25 Para-hydroxymandelic acid is an important intermediate in the preparation of antibiotics of the amoxicillin- en cephalosporin-type.

Ortho-hydroxymandelic acid can be used in the preparation 30 of the above-mentioned EDDHA, which is used *inter alia* as a sequestering agent. For that purpose, for instance the sodium salt of this isomer is treated with oxygen (in the presence of Pt/Pb as catalyst) to form sodium-2-hydroxy- $\alpha$ -oxobenzeneacetic acid, which can be converted to a double Schiff's base by a reaction with ethylene diamine. Reduction of this product with 35 hydrogen and a catalyst or with sodium borohydride, followed

by complexing with an iron(III) salt gives the agrochemical EDDHA-FeNa.

Ortho-hydroxymandelic acid can also be used as monomer in the polymer chemistry. For instance by copolymerization of 5 this isomer in the acid or alkaline form with formaldehyde, polymers with hydroxyl and carboxyl groups can be obtained. Depending on the degree of polymerization, such polymers are water-soluble or not. They can be used for the removal of heavy metal ions. Incidentally, in this polymerization ketal 10 formation between 2-hydroxymandelic acid and formaldehyde should be reckoned with. Water non-soluble polymers carrying carboxyl groups possess mildly catalytic properties for acid-catalyzed reactions and are useful as ion-exchanging resin.

The reaction of the 2-hydroxy- $\alpha$ -oxobenzeneacetic acid, to 15 be obtained from 2-hydroxymandelic acid, with ammonia/ammonium chloride gives 2-hydroxyphenylglycine after reduction of the Schiff's base with sodium borohydride. This compound is used inter alia in the preparation and chemiluminescence of 20 3-alkoxycarbamoylbenzo[b]furan-2(3H)-ones. In this connection reference is made to Lofthouse et al, J. Chem. Soc., Perkin I, (1979), 1634.

For the preparation of ortho-hydroxymandelic acid, heretofore no method of preparation was known that led to the desired results for industrial purposes.

25 Howe, Rao and Heyneker, for instance, according to their article in J. Chem. Soc. (C), (1967), 2510 obtained ortho-hydroxymandelic acid as a viscous gum which is difficult to process, through the reduction of 2-hydroxy- $\alpha$ -oxobenzeneacetic acid with hydrogen in an aqueous sodium hydrogen carbonate 30 solution in the presence of a prereduced Adams catalyst. An ether extract of this gum was found to contain still 20% diethyl ether, even after storage for 7 days under vacuum. As appears from the same article, previous attempts to obtain the ortho-isomer of hydroxymandelic acid had failed. It was for 35 instance proposed to treat salicylic aldehyde with hydrogen cyanide and to hydrolyze the resultant nitrile with

concentrated hydrochloric acid; to reduce 2-hydroxy- $\alpha$ -oxobenzeneacetic acid with sodium amalgam; and to diazotize the sodium salt of 2-aminomandelic acid and to heat the resultant diazonium compound with diluted sulfuric acid.

5 However, the reaction products were always obtained in a viscous form which is difficult to process and/or in a low yield.

Recently Hoefnagel, Peters and Van Bekkum have found that the reaction of phenol and glyoxylic acid to form hydroxy-10 mandelic acid need not necessarily be performed in an alkaline medium. In the above-mentioned article in Recl. Trav. Chim. Pays-Bas 107, (1988), 242-247, they describe that this reaction can be carried out under neutral conditions in an aqueous medium in the presence of different metal ions.

15 Depending on the catalyst used, different ortho/para ratios and different yield percentages are obtained. Catalysis by the use of bivalent metal ions typically results in a reaction product with an ortho/para ratio of 0.2-1.1, while catalysis with cations of a higher valency mainly leads to reaction 20 products with an ortho/para ratio of 1.3-28.

If a suitable method for separating the ortho- and para-isomers of hydroxymandelic acid were available, this method makes it possible to provide the ortho- and/or the para-isomer in the desired purity and yield, depending on the demand for 25 both or either of the isomers, by modifying the reaction conditions. The object of the present invention is to provide such a method.

From the above-mentioned article by Howe et al. it is known that acetone forms an adduct with ortho-hydroxymandelic 30 acid which is stable in acetone but is rapidly converted into ortho-hydroxymandelic acid in the presence of water. Such an adduct is not formed with para-hydroxymandelic acid. It has been found in practice that the isomers cannot be suitably separated in this manner because di-, tri- and other oligomers 35 are formed from the ortho-isomers. Thus, in the practice of

this separation method a great deal of desired product is lost because of these side reactions.

Surprisingly, it has now been found that the separation of a mixture comprising both the ortho- and the para-isomer of hydroxymandelic acid can be carried out very well by subjecting a mixture comprising the solid alkali metal salts of these isomers to an extraction step with a polar, aprotic, organic solvent. The alkali metal salt of the ortho-isomer has been found to be extremely soluble in such a solvent, as opposed to the para-isomer.

The method for separating the ortho- and para-isomers of hydroxymandelic acid or a salt thereof is characterized, according to the invention, by (a) starting from a mixture of ortho- and para-isomers in the alkali metal salt form or bringing a mixture of the ortho- and para-isomers into the alkali metal salt form; (b) extracting the mixture of the alkali metal salts with a polar, aprotic, organic solvent; (c) separating the polar, aprotic, organic solvent phase from the other (solid) phase, and (d) optionally recovering the ortho-isomer from the polar, aprotic, organic solvent phase, recovering the para-isomer from the other phase, and/or converting the alkali metal salts into the acid form or into a different salt form.

It will be clear that for a number of uses of the ortho- or the para-isomer of hydroxymandelic acid it is not necessary to further treat the two phases obtained from step (c). Thus, it is for instance possible to start from the solution of the alkali metal salt of the ortho-isomer in the polar, aprotic, organic solvent in a follow-up reaction. Method step (d) is therefore an optional step.

Further, it is clear that the separated isomer mixtures can be subjected to washing steps or other purification procedures.

Water is the most suitable medium in which hydroxy-  
35 mandelic acid can be formed. The reaction whereby

hydroxymandelic acid is formed can also be carried out in other solvents, for instance ethanol and dichloromethane.

For carrying out the separation method according to the invention, the ortho- and para-isomers of hydroxymandelic acid must be present in two different phases which can be simply separated. Preferably, for separating the two isomers one starts from a hydrous solvent including the alkali metal salts of both the ortho-isomer and the para-isomer. After evaporation of this mixture and addition of the polar, aprotic, organic solvent to be used according to the invention, in this case a two-phase system will form rapidly.

If the hydroxymandelic acid isomers in the starting mixture are not present in the alkali metal salt form, they can be simply brought into the desired form by treating the mixture with an aqueous alkali metal hydroxide solution.

The aqueous mixture of alkali metal salts of the isomers of hydroxymandelic acid can be extracted, after evaporation, with a suitable polar, aprotic, organic solvent, for instance acetone or methyl ethyl ketone.

In a preferred embodiment of the method according to the invention the water layer is evaporated as far as possible before method step (b) is carried out.

After evaporation of the water layer the resultant reaction mixture is extracted with a suitable polar, aprotic, organic solvent. Highly suitable polar, aprotic, organic solvents which can be used in accordance with the invention are acetone, methyl ethyl ketone, tetrahydrofuran and ethyl acetate. These solvents have been enumerated in order of preference.

A preferred embodiment of the method according to the invention is characterized in that acetone or methyl ethyl ketone is used as the polar, aprotic, organic solvent.

After the performance of a large number of experiments, it has been found that only separations of mixtures of alkali metal salts of ortho- and para-hydroxymandelic acid are possible through the (extreme) solubility of the adducts of

the ortho-isomer in the polar, aprotic solvent. Isomer mixtures in the form of, for instance, magnesium, calcium, barium and lanthanide salts cannot be separated through extraction in a corresponding manner.

5 It has further been found that the effectiveness of the separation depends on the size of the alkali metal cation. The following can be arranged in the order of effectiveness:  
 $K^+ > Na^+ > Rb^+ > Li^+, Cs^+$ . Accordingly, it is preferred that, as alkali metal salt of hydroxymandelic acid in method step  
10 (a), the potassium, sodium or rubidium form, preferably the potassium form, be used.

The solubility of the alkali metal salt of ortho-hydroxymandelic acid in polar, aprotic, organic solvents could be explained by assuming coordination of the two hydroxyl groups of the ortho-hydroxymandelic acid isomer with the alkali metal atom. It is impossible for such coordination to occur with the para-isomer. Further, by analogy with the formation of an adduct of acetone with ortho-hydroxymandelic acid, the solvent could play a role in this complexing as  
20 well.

As described above, the mixture of ortho- and para-isomers is preferably obtained by reacting phenol with glyoxylic acid under neutral conditions in the presence of a divalent or trivalent metal ion or an oxide thereof as catalyst. The point is that with this method it is possible under mild conditions to control the yield and the ortho/para ratio, depending on the need for both or either of the isomers.

The following table summarizes a number of specifics of process conditions that lead to the formation of ortho- and para-hydroxymandelic acid in certain proportions, the starting material always being 25 mmol glyoxylic acid. In this table "Cat/Gl" indicates the ratio in grams between the catalyst and glyoxylic acid. The ratios "phenol/Gl" and "ortho/para" are  
35 mole ratios.

TABLE

Catalyst	Cat/G1	Phenol/G1	°C	Reaction time (hours)	Initial pH	Yield %	Ortho/para
Al <sub>2</sub> O <sub>3</sub> calcined	0.82	3	80	24	6.8	35	0.23
Al <sub>2</sub> O <sub>3</sub> alkaline (Merck)	4.34	3	100	24	5.3	88	0.65
α-Al <sub>2</sub> O <sub>3</sub>	4.34	1	80	25	6.7	81	0.33
β-Al <sub>2</sub> O <sub>3</sub>	0.65	1	80	21	6.8	64	0.49
γ-Al <sub>2</sub> O <sub>3</sub>	4.34	3	80	48	6.7	81	0.20
Ga <sub>2</sub> O <sub>3</sub>	0.87	2	80	21	6.8	77	0.30
SiO <sub>2</sub>	0.43	3	100	30	6.9	80	0.28
Mg(OH) <sub>2</sub>	0.63	2	21	24	8.3	91	0.24
MgO	0.43	1.1	21	50	8.6	90	0.18
CuO	2.17	1	80	24	7.2	95	0.16
ZnO	0.04	3	80	3	7.2	95	0.30
Zn(OH) <sub>2</sub>	0.04	3	70	3	8.5	95	0.17
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	0.02	6	100	6	5.0	90	4.6
Al <sub>2</sub> (C <sub>2</sub> O <sub>4</sub> ) <sub>3</sub>	0.02	3	100	24	5.2	94	1.3
Zn C <sub>2</sub> O <sub>4</sub>	0.02	3	100	24	6.1	97	0.53

It is known that under the conditions outlined the metal ions used also catalyze the Cannizzaro reaction of glyoxylic acid. In this oxidation/reduction reaction hydroxyacetic acid and oxalic acid are formed from glyoxylic acid. This reaction 5 can be inhibited, for instance by adding an inert ligand, such as oxalate, to the reaction mixture.

Preferably, glyoxylic acid is reacted with an excess of phenol. An additional advantage of the excess of phenol resides in the fact that in that case disubstitution of the 10 phenol by glyoxylic acid is prevented as well. On the other hand, the excess phenol does have to be removed before the starting product is subjected to the separation method. This can be suitably effected by removing the excess phenol from the mixture by the use of extraction with diethyl ether.

15      Catalysis of the reaction between phenol and glyoxylic acid with bivalent metal ions typically results in a reaction product with an ortho/para ratio of 0.2-1.1, while catalysis with cations of a higher valence, in particular trivalent metal ions, mainly leads to reaction products with an 20 ortho/para ratio of 1.3-28. In order to obtain an optimum product mixture containing much hydroxymandelic acid substituted at the ortho position, it is preferred to use Al<sup>3+</sup> ions as catalyst. There exists an express preference for this catalyst, based on considerations regarding yield, ortho/para 25 ratio accessibility, cost price and environment.

The invention also relates to the para-isomer of hydroxymandelic acid or a salt thereof which has been recovered from the phase that remains after the separation of the polar, aprotic, organic solvent phase. This isomer can be 30 obtained from the aqueous phase in any of the conventional ways, for instance by acidifying the phase to pH 1.5, removing water, if any, by fractionated distillation under reduced pressure and lixiviating the residue with ethyl acetate or extracting it with diethyl ether. The desired product can 35 subsequently be isolated by removing the ethyl acetate or the ethanol.

The invention further relates to the ortho-isomer of hydroxymandelic acid or a salt thereof, which has been recovered from the polar, aprotic, organic solvent phase obtained from the separation method according to the 5 invention. For that purpose, the solvent phase can be evaporated, whereby a voluminous white foam is obtained. This white foam, which will typically still contain a (minor) amount of solvent, is subsequently dissolved in a small amount of water and the liquid phase is evaporated again. Finally, a 10 hygroscopic product is left.

Finally, the invention relates to a method for the preparation of EDDHA, which method is characterized according to the invention by the use of the ortho-isomer obtained in accordance with the invention. In principle, EDDHA can be 15 prepared in various ways from ortho-hydroxymandelic acid. Ortho-hydroxymandelic acid is often oxidized in a first step, for instance analogously to the disclosure of DE-OS-2,824,407.

#### Example 1

To a mixture of 56.4 g (0.60 mol) phenol, 9.20 g 20 (0.10 mol) glyoxylic acid and 4.08 g (0.102 mol) sodium hydroxide in 20 ml water, a solution of 666 mg (0.001 mol)  $\text{Al}_2(\text{SO}_4)_3 \cdot 18 \text{H}_2\text{O}$  in 10 ml water was added. Under a nitrogenous atmosphere, the reaction mixture was boiled for 6 hours under reflux cooling, whereby a bright yellow reaction mixture was 25 obtained. After cooling to room temperature the pH was adjusted to 7 by adding 2.8 ml of an aqueous 2 M sodium hydroxide solution. The turbid reaction mixture was extracted three times with 35 ml portions of diethyl ether for removing the excess phenol. After drying and evaporation of the 30 ethereal solution, 47.2 g phenol was obtained.

The phenol-free fraction was further processed by acidifying the water layer with 18 N sulfuric acid to a pH of 0.7, adding 25 g sodium chloride, and extracting with three 35 ml portions ethyl acetate. Without drying the ethyl acetate solution was evaporated and after adding 10 ml water the

turbid solution was evaporated again to remove the enclosed ethyl acetate and the greater part of the water. The resultant viscous oil, after being dried to constant weight, weighed 12.75 g (76%). HPLC analysis of the viscous residue 5 demonstrated the presence of 14% para-hydroxymandelic acid, 5% dimerec product and 81% ortho-hydroxymandelic acid. The HPLC analysis was carried out with the use of a Waters Associates Chromatography Pump M-45, Differential Refractometer RI 401, Autoinjector Perkin-Elmer ISS 100 and a Spectrophysics SP 4100 10 Integrator. As column material, C18 Nucleosil® RCM 100 module was employed. Methanol/water/trifluoroacetic acid 10/90/0.1 was used as eluent. The observed retention times were: 4.7 minutes for 2,6-disubstituted mandelic acid, 5.2 minutes for para-hydroxymandelic acid + 2,4-disubstituted mandelic 15 acid and 7.7 minutes for ortho-hydroxymandelic acid.

Example 2

The procedure according to Example 1 was carried out again, but the further processing was now such that no oligomerization reaction occurred.

20 After removal of the excess phenol by extraction with diethyl ether, the water layer was evaporated without acidifying with sulfuric acid, which yielded 19.2 g of a light-yellow powder (mixture A), a mixture of sodium salts.

Mixture A was subsequently extracted with 100 ml 96% 25 ethanol, whereby an insoluble water product was obtained. This product, (mixture B), was filtered off and weighed 1.7 g. This mixture was found to contain sodium sulfate and the aluminum complex of ortho- and para-hydroxymandelic acid (1:1).

The filtrate obtained gave 17.4 g light-yellow powder 30 (mixture C). Mixture C was introduced into 40 ml 90% acetone, whereafter a precipitate was formed by adding 5 portions of 100 ml acetone. This precipitate consisted of the ortho- and para-isomers in a proportion of about 1:1. Filtering off and extraction with 3 portions of 100 ml acetone yielded 3.2 g 35 insoluble product (mixture D). Evaporation of the two combined

acetone-containing filtrates yielded 14.2 g solid residue (mixture E). In a concentrated solution of mixture E in 50 ml acetone, a precipitate of practically pure ortho-isomer formed after standing for some time at room temperature. Filtering off daily yielded, after 5 days, a total of 3.6 g white powder (product F), the acetone-insoluble form of the sodium salt of 2-hydroxymandelic acid.

After evaporation of the substrate, followed by solution in 15 ml water and addition of 135 ml acetone, the thus obtained turbid solution was boiled with reflux cooling for 5 minutes. Then the mixture was allowed to cool overnight to room temperature. Filtering this product off yielded 0.8 g substantially pure 4-hydroxymandelic acid (H). Evaporation of the filtrate, followed by solution in 30 ml acetone, filtration and evaporation, yielded 9.0 g pure sodium salt of the 2-hydroxymandelic acid (product G) as a white voluminous foam containing 0.3 mol acetone per mole compound. An aqueous solution of this foam, after evaporation, yielded a glassy product which was free from acetone.

Mixture D, upon further processing in a second preparation, yielded another 1 g of the two compounds, which corresponds with an additional yield of 5%.

HPLC analysis of the products yielded the following specifics:

25	mixture A:	18.8% para	80.0% ortho	1.2% disubstituted
	mixture B:	28.0% para	66.0% ortho	6.0% disubstituted
	mixture C:	17.7% para	81.5% ortho	0.8% disubstituted
	mixture D:	50.0% para	40.0% ortho	10 % disubstituted
	mixture E:	12.3% para	87.2% ortho	0.5% disubstituted
30	mixture F:	2.7% para	97.1% ortho	
	mixture G:	NMR analysis	> 96% ortho	
	mixture H:	NMR analysis	> 95% para	

D<sub>e</sub> NMR analysis was carried out in D<sub>2</sub>O with the aid of a Nicolet NT-200 WB appliance.

Example 3

To a mixture of 7.06 g (75 mmol) phenol, 2.30 g (25 mmol) glyoxylic acid ( $\text{HC=OCOOH}\cdot\text{H}_2\text{O}$ ) and 1.40 g (25 mmol) potassium hydroxide in 50 ml water, 77 mg (0.5 mmol) zinc oxalate was 5 added. This mixture was allowed to boil with reflux cooling for 6 hours. After evaporation of the water layer, 5.5 g of a mixture containing 35.1% ortho compound and 64.9% para compound was obtained.

Extraction with acetone (3x 200 ml), after evaporation, 10 gave 1.43 g white foam which, in addition to a small amount of acetone, comprised approximately 3% para-isomer and 97% ortho compound. The insoluble product, 3.5 g (5% ortho-isomer and 95% para-isomer), after extraction with 96% ethanol (2x 50 ml), gave 3.1 g practically pure potassium salt of para- 15 hydroxymandelic acid as a fine powder which contained a small amount of inorganic material, mainly zinc hydroxymandelic acid complex and zinc oxalate. After evaporation of the filtrate, a mixture of potassium salts of the ortho- and para-isomers (0.4 g) remained. This mixture can be added to a reaction 20 mixture of a subsequent preparation before it is subjected to the separation method according to the invention.

Example 4

Example 3 was in essence repeated, utilizing other zinc compounds as catalyst. After evaporation of the water layer 25 and extraction with acetone, the potassium salts of para- and ortho-hydroxymandelic acid are obtained in high purity. The table below specifies the catalysts used, the reaction conditions used and the yields of the isolated hydroxymandelic acid salts:

Catalyst	pH	Reaction time	Reaction temp.	Yield 4-OH	Yield 2-OH
zinc oxide	8.52	3 hours	70°C	77%	15%
5 zinc chloride	8.52	3 hours	70°C	74%	12%
zinc acetate	8.52	3 hours	70°C	75%	15%
zinc acetate	6.13	24 hours	100°C	58%	28%
zinc acetate	6.25	6 hours	100°C	60%	26%

Example 5

10 In accordance with the method described in DE-OS-2,824,407, 5.70 g (30 mmol) sodium-2-hydroxymandelate, obtained from the method according to Example 2, was oxidized in a 0.2 M sodium hydroxide solution at a temperature of 70°C in the presence of 5% platinum on active carbon and  $\text{Pb}(\text{NO}_3)_2$ .

15 The reaction was monitored with HPLC. After 2 days 92% of the hydroxymandelate salt was found to have been converted to 2-hydroxy- $\alpha$ -oxobenzeneacetic acid. This compound was isolated and purified in the manner described in the DE-OS referred to.

Then 332 mg of this purified compound was dissolved in  
20 1.5 ml methanol. This solution was added to a solution of 60 mg ethylene diamine and 1.5 ml methanol. During 1 hour stirring, a precipitate was formed, which was removed by filtration, whereby 230 mg (65%) of the double Schiff's base of the benzeneacetic acid was obtained. This Schiff's base had  
25 a decomposition point of 151-152°C.

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ,  $\text{pD}=10.29$ )  $\delta$ (ppm): 175.27, 169.65, 169.18, 136.51, 132.60, 121.18, 119.04, 115.23, and 51.41.

To obtain ethylene diamine-N,N'-di-(2-hydroxyphenyl-acetic acid), EDDHA, 332 mg 2-hydroxy- $\alpha$ -oxobenzeneacetic acid  
30 was dissolved in 2 ml 2 M caustic soda. To this 60 mg ethylene diamine was added. Then this mixture was reduced at 5°C with

portioned addition of 102 mg sodium borohydride. Thus a clear light-yellow solution was obtained, which was neutralized with 2.75 ml 2 M hydrochloric acid. The precipitate was removed by filtration after standing overnight at room temperature.

- 5       Washing with water and methanol gave 180 mg (47%) EDDHA, melting point 228-230°C.

According to NMR analysis (Varian T 60, 25°C), the filtrate contained approximately 35% ethylene diamine-N-2-hydroxybenzeneacetic acid and approximately 15% of the  
10      ethylene diamine salt of 2-hydroxymandelic acid. Both products can be added in a second preparation cycle of EDDHA.

CLAIMS

1. A method for separating the ortho- and para-isomers of hydroxymandelic acid or a salt thereof, comprising the steps of (a) starting from a mixture of ortho- and para-isomers in the substantially solid alkali metal salt form, or bringing a mixture of the ortho- and para-isomers into a substantially solid alkali metal salt form; (b) extracting the mixture of the alkali metal salts with a polar, aprotic, organic solvent; (c) separating the polar, aprotic, organic solvent phase from the other phase, and (d) optionally recovering the ortho-isomer from the polar, aprotic, organic solvent phase, recovering the para-isomer from the other phase, and/or converting the alkali metal salts to the acid form or to a different salt form.
2. A method according to claim 1, wherein the starting material is a mixture of the ortho-isomer and the para-isomer of hydroxymandelic acid in the alkali metal salt form in a hydrous solvent, and the water layer is evaporated as far as possible before method step (b) is carried out.
3. A method according to any one of claims 1 or 2, wherein acetone, methyl ethyl ketone, tetrahydrofuran or ethyl acetate is used as the polar, aprotic, organic solvent.
4. A method according to any one of claims 1-3, wherein acetone or methyl ethyl ketone is used as the polar, aprotic, organic solvent.
5. A method according to any one of claims 1-4, wherein acetone is used as the polar, aprotic, organic solvent.
6. A method according to any one of claims 1-5, wherein as alkali metal salt of hydroxymandelic acid in method step (a) the potassium, sodium or rubidium form is selected.
7. A method according to any one of claims 1-6, wherein as alkali metal salt of hydroxymandelic acid in method step (a) the potassium form is selected.

8. A method according to any one of claims 1-7, wherein the starting material is a mixture of ortho- and para-isomers which has been obtained by reacting phenol with glyoxylic acid in the presence of a divalent or trivalent metal ion or an oxide thereof as catalyst.
- 5 9. A method according to claim 8, wherein glyoxylic acid is reacted with an excess of phenol.
10. A method according to claim 8 or 9, wherein  $\text{Al}^{3+}$  ions are used as catalyst.
- 10 11. A method according to any one of claims 8-10, wherein the reaction mixture obtained is neutralized with the aid of an alkali metal hydroxide.
- 15 12. A method according to any one of claims 8-11, wherein the excess phenol is removed from the mixture by extraction with diethyl ether.
13. Para-isomer of hydroxymandelic acid or a salt thereof, recovered from the solid phase obtained from the method according to any one of claims 1-12.
14. Ortho-isomer of hydroxymandelic acid or a salt thereof, recovered from the polar, aprotic, organic solvent phase obtained from the method according to any one of claims 1-12.
- 20 15. A method for the preparation of EDDHA, wherein the starting material is the ortho-isomer of hydroxymandelic acid according to claim 14.

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/NL 93/00277

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 C07C59/52 C07C51/48 C07C51/487 C07B57/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,81 00404 (BEECHAM GROUP LTD.) 19 February 1981 see page 3, line 3 - line 13 see page 7; example 4 see page 10; example 10 see claims 1-4 ---	1,2,4,6, 8,10
Y	PATENT ABSTRACTS OF JAPAN vol. 4, no. 155 (C-29)(637) 29 October 1980 & JP,A,55 102 537 (NIPPON GOSEI KAGAKU KOGYO K.K.) 5 August 1980 see abstract ---	1,2,4,6, 8,10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

8 April 1994

Date of mailing of the international search report

28.04.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Klag, M

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/NL 93/00277

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 5, no. 188 (C-81)(860) 27 November 1981 & JP,A,56 110 643 (UBE KOSAN K.K.) 1 September 1981 see abstract -----	1,2,4,6, 8,10

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/NL 93/00277

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8100404	19-02-81	AT-T-	3408	15-06-83
		AU-B-	538368	09-08-84
		AU-A-	6124480	03-03-81
		EP-A, B	0024181	25-02-81
		US-A-	4368334	11-01-83